Electrophysiological sequelae of inflammatory demyelination

Wilfred A Nix

Nerve fibres handle information by electrical signals travelling over the nerve. This process can be monitored by electrophysiological examination (nerve conduction studies or evoked potentials) which help to identify acute nerve fibre malfunction and to monitor restitution of function or improvement of chronic functional impairment. The studies give qualitative and more important quantitative information about the functional deficit.

For prognostic purposes these studies are helpful to disclose clinically inaccessible lesions. They may differentiate the lesion as axono- or myelinopathy. This classifies the primary pathological change but does not help to clarify the pathophysiological mechanism of the lesion. Electrophysiology can prove in autoimmune diseases, such as multiple sclerosis (MS), the lesions to be located mainly in the CNS, and in acute inflammatory polyradiculoneuropathy (AIDP) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the peripheral nervous system (PNS).

The value of different established evoked potential methods for the diagnosis of MS will be discussed. New insights have been gained in the electrophysiology of AIDP and CIDP. Due to the easier accessibility to the peripheral nerve sequels of demyelination they can be studied in more detail and the basic findings can be taken to be valid for all myelinated structures of the nervous system. These facts are of value in understanding the diagnostic potential of electrophysiological methods for decision making in diagnosis, therapy and in follow up studies in both situations.

Evoked potential studies in MS

In multiple sclerosis there is demyelination in the CNS. These lesions do not always result in clinically obvious symptoms. In patients with an established diagnosis of MS, electrophysiological tests are seldom useful for confirmation of the diagnosis. Studies can help to monitor disease progression, especially to detect new lesions. The situation is different when the diagnosis is not yet definite. Here evoked potential studies can contribute to the evaluation of the patient’s disease status.12

The most sensitive studies are the visual evoked potentials (VEP). After optic neuritis they disclose in about 93% changes as sequels of de- and remyelination. These changes are permanent deficits and can identify an old optic nerve lesion in a clinically normal visual system. This is helpful for the clinician as electrophysiology can prove a previous clinical event. Structural lesions can also be documented with MRI.3 Not all lesions disclosed by MRI result in functional impairment of nerve conduction nor do electrophysiological impairments need to have a radiologically detectable correlate. MRI and electrophysiology are supplementary as they disclose different structural and functional aspects of lesions within a tissue.

The high diagnostic yield of VEP has been shown by Chiappa2 where 85% of patients with a definite diagnosis of MS had pathological VEP findings. This is also true to a similar extent for sensory evoked potentials (SSEP) and brainstem auditory evoked potentials (BAEP). SSEPs can be recorded after upper or lower limb stimulation. Upper limb SSEPs are abnormal in about 60% of all MS patients. The diagnostic yield of lower limb stimulation is higher because of the greater length of CNS white matter involved. In MS, BAEP abnormalities consist mainly of loss of amplitude of wave V (55%), prolonged interwave separation (13%), or both (33%).

Magnetic stimulation of the cortex induces evoked motor potentials (MEP) in arm, hand, leg or foot muscles. Additional stimulation of the nerve roots enables the calculation of the central motor conduction time. Different studies prove that this method has an equivalent high diagnostic specificity and sensitivity as VEPs and SSEPs.1 In a few patients with CIDP subscleral involvement can be shown by prolonged central motor conduction times. The association of a multiple sclerosis like syndrome with CIDP is rare.4

The four evoked potential studies that have been mentioned are complementary. One test may reveal evidence of a clinically unsuspected lesion while the other three do not. It is useful to do all four tests especially in difficult cases.

Pathophysiological considerations of nerve conduction

In polineuropathies with axonal damage, nerve conduction studies show mildly impaired conduction velocities with impaired action potential amplitude and demervation activity in muscles. Clearly, secondary or primary demyelination can occur and influence the diseases, electrodagnostic appearance
with apparent focal conduction block or marked slowing of the nerve conduction. Isolated conduction block inhibits transmission of electrical impulses over a focal demyelinating lesion. The proximal and distal nerve segments are capable of normal conduction. AIDP and CIDP affect primarily myelin or the myelin-producing Schwann cell. These structures can be affected by oedema of the node of Ranvier area by disease-associated metabolic disturbances. This reason for an alteration of nerve conduction with conduction block can quickly resolve either spontaneously or due to therapy and may dramatically change the clinical picture. This is different for primary destruction of the myelin sheath. It usually leaves the axon intact but impairs over a longer time nerve conduction or leads to conduction block. Due to the preserved axon there is no denervation activity in the muscle. Restitution of function is achieved by remyelination, which for the nervous system is a fast and efficient process. It is usually complete within four to six months from the peak of an illness. In the case of fulminant inflammation the axon can undergo degeneration which will be accompanied by denervation activity in the muscle. Restitution of function in this case involves the slow (1 mm/day) and often inefficient process of axonal regeneration.

Some autoimmune diseases like lupus erythematosus may be associated with vasculitis that can induce vascular injury impairing circulation in the peripheral nerve. In these cases the effect is the same as in diabetes, where some nerve fibre damage is believed to result from local ischaemia. Occluded small arteries at one level in a nerve induce ischaemia to an entire segment of nerve that can clinically be manifested as a focal mononeuropathy. If multiple levels of several nerves are affected, a diffuse patchy neuropathy, a multiple mononeuropathy can result. Multiple lesions may summate to produce a clinical picture of bilateral distal symmetric nerve involvement mimicking a distal axonopathy.

**Acute and chronic inflammatory polyneuropathy**

Acute inflammatory demyelinating polyradiculopathy is a rapidly evolving disease, and presumed to be an autoimmune reaction. The Guillain–Barré syndrome that once appeared to be a distinct clinical entity may be the consequence of different pathological processes that produce a similar clinical picture. The early stage of AIDP may be difficult to identify and has no pathognomonic features, but the fully evolved pattern can be easily recognised by clinical and electrophysiological features. The primary lesions are confined to the PNS. Within about three weeks of onset of demyelination, Schwann-cell proliferation starts, a prerequisite of remyelination of the denuded axons. Electrophysiology monitors these events and the results can be compared with the clinical status of the patient. An electrodiagnostic protocol for the evaluation of patients with AIDP has been proposed.

In AIDP motor nerves are far more affected by demyelination than sensory or autonomic fibres. Demyelination occurs in the beginning rather focally then diffusely at different levels of the peripheral nerves. Various findings can be expected ranging from normal to reduced nerve conduction velocity, abnormal compound muscle action potential with increased duration or altered waveform. If on proximal after distal stimulation there is a considerable loss of CMAP amplitude this indicates a partial conduction block. Further findings are prolonged distal motor latencies or F-wave and H-reflex abnormalities. The nerve lesion is not uniformly distributed between the nerve root and the motor point. The earliest disturbances are found in the most proximal and most distal sites of the axon. This are the ventral roots fibres, or the intramuscular abstractions of the nerve twigs. Evidence is needed to establish if this distribution of lesions can be explained by local normal or acquired deficiencies in the blood-nerve barriers. Later demyelination affects other areas of the nerve trunk. Demyelination or conduction block occurs disproportionately at nerve sites that are known to be the site for pressure palsies or entrapment lesions. In a series of 180 patients criteria for demyelination were met in 87% during the first five weeks. Motor nerve conduction abnormalities were found as early as the second week, and the sensory conduction was slowest in the fourth week. An interesting finding was that 52% had normal sural nerve conduction but impaired sensory median nerve velocities that distinguishes this illness from other acute or chronic polyneuropathies. A total of 36% of patients had symptoms of autonomic instability. In a series of 113 patients 37% had initially normal sensory conduction studies. Twenty seven per cent had normal motor conduction with conduction block, 27% decreased motor conduction together with conduction block, and 22% generalised conduction slowing.

CIDP needs to be distinguished from AIDP by clinical symptoms, laboratory tests including cerebrospinal fluid examination, and nerve biopsy findings. Electrodiagnostic studies are an important marker but in CIDP can display similar features to AIDP. Diagnostic criteria published by the American Academy of Neurology are very helpful in defining required features for the clinical and electrophysiological diagnosis.

**Paradoxical clinical and electrophysiological findings in acute AIDP**

At the early stage of AIDP there is no correlation between motor conduction velocity and severity of the disease. In long nerves there is a greater likelihood of involvement than in short nerves. With time, the early clinical finding of motor weakness often
resolves. This is possibly due to resolution of conduction blocks. Over time the myelin attack has changed from a focal event to a more generalised problem. This is why in spite of resolution of motor weakness paradoxically nerve conduction velocities become slower. A study showed that abnormalities of nerve conduction velocity in recovered patients at the twentieth week, were similar to disturbances at week two, where patients were clinically severely affected.

In several studies the amplitude of the M response early in the diseases has proved to be a helpful parameter for prognosis. Even if quickly declining amplitudes are supposed to indicate a severe course of illness and a slow recovery. Restitution of nerve function is associated with improvement of CMAP. The repeated measurement of CMAP after distal nerve stimulation in different nerves is a helpful parameter to monitor nerve function in AIDP.

**Prognostic considerations**

For prognostic purposes electromyography (EMG) can play a helpful role. In patients with severe demyelination axonal damage can occur with demyelination of muscle fibres and positive sharp waves or fibrillations on EMG examination. The early occurrence of denervation activity does not indicate the severity of the disease but suggests that the nerve lesions must be very proximal to the muscle. This is because the length of the nerve stump attached to a muscle in a severed nerve determines the timespan over which denervation activity occurs after a nerve lesion. In this situation prognosis is dependent on axonal regeneration and the distance the axon has to bridge. Even if regeneration is successful over distance, the axon may reinervate inappropriate targets, resulting in abnormal function. Reports which indicate poor outcome with early and prominent spontaneous activity outnumber those where such a correlation was not found. There are about 3% of cases with AIDP that have a different course of illness. Near onset motor nerves display a low CMAP amplitude or are even inexcitable. These neuropsychological signs are indicative of extensive axonal degeneration and could be signs of a primary axonal attack as suggested in histological studies. This could represent a "bystander effect" secondary to inflammatory infiltration and demyelination as shown in other pathological studies. These patients, often published as case reports or in small numbers, were until recently believed to have a bad prognosis with permanent severe neurological deficits. In a follow up study of 34 patients it is shown that the initial loss of excitability of motor nerves and active denervation cannot be used to predict the outcome. In eight patients with inexcitable motor nerves in the beginning of the illness only three had residual disability at 12 months. The others had completely recovered. However, consecutive studies of CMAP amplitude have prognostic values. Increasing amplitudes signal a good prognosis, delayed inexcitability suggest poor outcome. In CIDP the CMAP can be used to monitor the effect of immunoglobulin or plasma therapy. The therapeutic effect was an increase of the amplitude. These quick changes after therapy hint at altered myelin properties or changes at the node of Ranvier.

**Diagnostic problems and impact of conduction block**

It is not always easy to define the reasons for a drop in CMAP. Partial conduction is present when area or amplitude of a CMAP is reduced with proximal stimulation, compared with the response to distal stimulation. There is still a great deal of controversy on how to diagnose a partial conduction block, especially in chronic neuropathies. One point of discussion is on the magnitude of CMAP reduction necessary to define a conduction block. Opinions range between a reduction of 20–60%. The problem involved is temporal dispersion that might not play a role in the first days of the acute stage of a disease but later. When demyelinating neuropathy has progressed for a few days, the range of conduction velocities within a nerve increases considerably. In such instances motor units will be activated at different times, and their desynchronised action potentials can induce an interphase cancellation within the CMAP. This causes a reduction of the CMAP amplitude and area and often increases the CMAP duration. The CMAP duration after proximal stimulation should therefore not exceed an increase of 15%. Guidelines on how to manage the problems involved have recently been published.

Persistent and transient conduction blocks are also found in multifocal conduction block neuropathies which can mimic motor neuron disease. One possible cause for this neuropathy is an autoimmune disorder that alters myelin function. As the two disorders cannot be separated on clinical grounds and the nerve conduction studies and defined diagnostic criteria are of the utmost importance.

**Conclusion**

Electrophysiological studies of the peripheral and central nervous system play an important part in the evaluation of patients with suspected autoimmune diseases. Diagnosis can only be established when clinical findings are supported by diagnostic procedures including neuropsychological studies. Demyelination and ensuing remyelination influences conduction properties of nerve fibres that can still be detected years after the acute phase. In the acute phase there are functional and morphological disturbances of different aetiology that all have the same effect, of altering nerve conduction properties. The resolution of conduction block within the first weeks of an illness like AIDP may considerably improve the patient's motor function. This
may contrast with the steadily deteriorating nerve conduction velocities. In these situations there is no correlation between electrodiagnostic findings and the patient's clinical status. This has also to be considered when clinical trials are performed.